IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re Application of
Karl Kolter et al.
Serial No.09 /811,546
Filed: March 20, 2001
For: Solid oral dosage forms with delayed release of active ingredient and high mechanical stability

D E C L A R A T I O N

I, Karl Kolter, Dr. rer. Nat., a citizen of Germany and a resident of Sudetenstrasse 1, 67117 Limburgerhof, Germany, hereby declare and say as follows:

I am a fully trained pharmacist, having studied pharmacy at Mainz University in the period of from 1976 to 1981.

I was awarded my PhD in Mainz, where in the period of from 1981 to 1985 I worked as an assistant at Mainz University.

I joined Knoll AG, a former subsidiary of BASF Aktiengesellschaft, located in 67061 Ludwigshafen, in 1986 , where I have been engaged in research and development in the field of pharmaceutical formulations.

In 1993 I joined BASF Aktiengesellschaft, now named BASF SE, and I have since been engaged in the field of development of pharmaceutical excipients and formulations of active ingredients.

I am a co-inventor to Application Serial No. 09 /811,546;

I have carefully studied the final Office Action of September 17, 2008 and the rejection of the claims under 35 U.S.C. §112, 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a).

Now, hereby, I want to state the following:

Regarding the rejection under of claim 30 under 35 U.S.C. §112, I want to point out that contrary to the submission as of page 3, last paragraph, that the additives such as fatty alcohols, glycerides, waxes etc. are allegedly lipophobic, these are indeed lipophilic additives. As is well known to a person of ordinary skill in the art the said additives cited in the present application are insoluble or practically insoluble in water, but are readily soluble for instance in hydrocarbons which is a typical solubility behavior of lipophilic substances.

Regarding the rejection of claims 1, 4, 7-12, 14, 16-18, 22,24 and 31-33 under 35 U.S.C. § 102(b) over Ortega (US 4,837,032) I want to explain that Ortega does not teach pre-formulated mixtures of PVAc / PVP according to the claimed invention.

The pre-formulated mixture of PVAc/PVP is an intimate mixture of the two constituents which is obtained as described in US patent No. 5,490,990, cited on page 3, line 17-21 of the present application by spray-drying a dispersion containing the two polymeric components. In such a pre-formulated mixture the constituents cannot be separated by mechanical operations such as for instance sieving. Also, when examined under a light microscope the two constituents cannot be separated mechanically and cannot be distinguished as two different components.

Ortega discloses that an overall composition that preferably comprises polyvinyl acetate as water insoluble polymer, polyvinyl pyrrolidone as water soluble film forming polymer and cellulose actetate phthalate as acid soluble polymer. According to Ortega the tablet are preferably obtained by (a) wet granulating a mixture of the active ingredient cellulose acetate phthalate with an organic solution containing a part of the polyvinyl pyrrolidone, (b) mixing the remaining part of the polyvinyl pyrrolidone with the polyvinyl acetate and (c) mixing the compositions (a) and (b) followed by tabletting the overall composition (see col. 2, lines 32 - 42 and Claim12. According to col. 4, lines 4-10, the granules obtained according to step (a) may be mixed with the remaining film former and the water insoluble polymer. Example 1 of Ortega describes a process wherein first of all granulate of active ingredient, cellulose acetate phthalate and polyvinyl pyrrolidone is prepared. The dried granulate is transferred to a V-blender, polyvinyl acetate, another portion of polyvinyl pyrrolidone and a lubricant mix are added and the ingredients are all mixed together and then pressed to tablets.

However, to a skilled person Ortega does not disclose that polyvinyl acetate and all of the polyvinyl pyrrolidone are pre-formulated to give an intimate mixture wherein the two components cannot be separated mechanically. Even though it is mentioned that polyvinyl pyrrolidone and polyvinyl acetate can be mixed and subsequently be admixed with the active

ingredient containing granulate a skilled person would not understand this disclosure in such a way that a pre-formulated mixture is produced or intended. Mere mixing of components for instance in a V-blender does not lead to pre-formulated mixtures as used according to the claimed invention. According to Example 1 the second portion of the polyvinyl pyrrolidone is admixed with the granulate of step (a) and the polyvinyl acetate by normal mechanical mixing in a V-blender. In other words, Ortega does not disclose the same binder.

Regarding the rejections under § 103(a) over Kolter et al. and Ortega or Kolter et al., Ortega and Matthews (US 4,816,259) I first of all want to explain about the specific features of the invention and the problems associated with the presently claimed invention.

The claimed invention is concerned with solid oral dosage forms, preferably tablets, for delayed release of an active ingredient from a matrix. Such oral dosage forms should at the same time have a high mechanical stability. Delayed release means that it takes at least three hours for 80 % of the active ingredient being released from the dosage form. By contrast, in instant release dosage forms the active ingredient is completely released after one hour.

The delayed release tablets ought to be mechanically stable in order to avoid abrasion and breakage during coating and packaging. Also, abrasion and friction of the matrix in the gastrointestinal tract may negatively influence the release characteristics. Without sufficient mechanical stability of the tablets a reliable application of a fixed dosis is not possible. Suitable tablets should show a tablet hardness of at least 200 Newton.

As regards the claim rejections of Claims 1, 3-14,16-18, 22-24 and 27-33over Kolter et al. in view of Ortega I want to state as follows:

According to the Office Action of September 17, 2007, page 5, paragraph1. (2) it is acknowledged that the reference US 6,066,334, Kolter et al., to which I am a co-inventor does not teach the claimed release rate.

The Examiner argues however that Ortega teaches that the amount of binder is a result-effective parameter that could be altered to vary the release rate based on the intended use of the final product.

The Kolter reference clearly relates to instant release where the active ingredient is completely released after one hour.

Ortega however teaches a different binder system useful for delayed release and consisting of an obligatory combination of three components, i.e. cellulose actetate phthalate, polyvinyl acetate and polyvinyl pyrrolidone, preferably in amounts such that a tablet contains 15 weight percents of each of these three components. The resulting tablets shall have a hardness of 4 to 10 kg (Erweka Tester) which is an equivalent to a tablet hardness in Newton of 40 to 100 Newton.
A tablet hardness of 40 to 100 Newton is far below the level which a skilled person would consider as a satisfying.

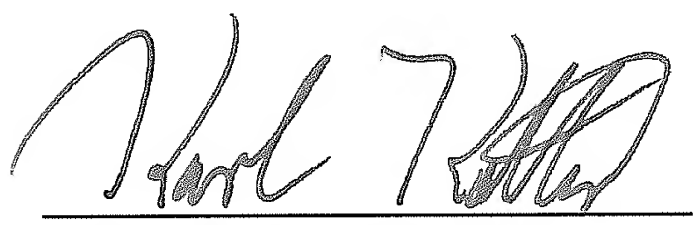
As an ordinarily skilled expert I would not have been motivated to adapt the composition taught by Ortega first of all because the tablets obtained using such compositions clearly lack in tablet hardness. Also, such an adaptation would not only be a variation of amounts but also would mean to eliminate a very specific component, i.e. the cellulose acetate phthalate, a component which Ortega includes as an obligatory component, plus using a composition that differs essentially form the Ortega composition in that it is pre-formulated mixture. Therefore it is my belief that such a complex variation, namely of taking different amounts of a different type of binder which was known for a different use and at the same time eliminate an obligatory component, was not obvious and it was not to be expected that such a variation would be successful.

Regarding the rejection of Claims 1, 3-14,16-18, 22-24 and 27-34 over Kolter in view of Ortega in view of Matthews, US 4,816,259, I want to point out that the Matthews reference discloses a new process for enterically coating soft gelatin capsules and deals inter alia with the specific difficulties of coating the smooth surfaces of such capsules.
In the description of the background to the Matthews invention in Col. 1 it is mentioned that numerous coating solutions have been used in the past. A number of quite different prior art coating materials are then recited, amongst others polyvinyl acetate and polyvinyl pyrrolidone. It is only very generally mentioned that coatings are commonly applied to dosage forms for various reasons such as protecting ingredients, improve appearance, taste masking, control site of action of the active ingredients etc.. There is no indication whatsoever in the disclosure of Matthews, that a specific combination of just two coatings out of that list, namely polyvinyl acetate and polyvinyl pyrrolidone, could in any way have advantageous effects. Insofar it is my opinion as an expert of ordinary skill in the art that Matthews does not at all teach advantages stemming from such a coating and that therefore such a combination would not have been obvious.

This was in my opinion not to be expected.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so are made punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at 67056 Ludwigshafen, Germany, this 23rd day of February 2009.



Signature of Declarant